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TITLE: Treating Gulf War Illness with Novel Anti-Inflammatories: A Screening of Botanical Microglia Modulators

PRINCIPAL INVESTIGATOR: Jarred Younger, PhD

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Since the last annual report, we have continued with periodic advertising, recruitment, participant screening, participant enrollment, and the study protocol.

All start up subtasks have been completed. The study treatment compounds have been purchased, and the blinded capsules have been created and prepared into randomized lines.

To date, 222 potential participants have filled out the online screening questionnaire, 129 of those have been screened by telephone, and 34 participants have enrolled into the study, and 3 have re-enrolled. 5 other potential participants have been identified as meeting initial eligibility requirements, and we expect to meet our end goal number during the next reporting period. We have been approved to enroll participants with diabetes. These participants were originally excluded because 4/9 botanicals were thought to have possible interactions with diabetic medications. We have developed a block randomization system to ensure that these 4 botanicals are not given to diabetic participants. In addition, we have obtained IRB approval to begin the process of re-enrollement as of September 2017. We have had a change of personnel; we have completed IRB approval to switch our medical monitor whose role will be to serve as an additional safety mechanism from Jessica Merlin to Dr. John Rinker associate professor of the Department of Neurology at UAB. We will continue to work towards the following milestones: 40 GWI participants enrolled and 40 GWI participants completed entire protocol.

15. SUBJECT TERMS Gulf War Illness, botanical, anti-inflammatory, biomarker, microglia, improvement, treatment					
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1. **INTRODUCTION:**

The major aim of this research project is to identify the most promising botanical anti-inflammatories for the treatment of Gulf War Illness (GWI). A second, exploratory, aim is to identify biomarkers of GWI improvement. To accomplish those aims at the University of Alabama at Birmingham, we are recruiting 40 male veterans diagnosed with GWI. Each participant will receive three different botanical compounds and placebo over a 300 day period. Each participant will also participate in a 30-day baseline period starting the first month to report their individual daily GWI symptom severity ratings. Analyses will then be conducted to identify the most effective botanical compound that reduced microglia hyper excitability. Ultimately, this information may be used to develop new treatments that specifically target the pathophysiological mechanisms of Gulf War Illness.

2. **KEYWORDS:**

Gulf War Illness, botanical, anti-inflammatory, biomarker, microglia, improvement, treatment

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project? & What was accomplished under these goals?**

  - Task 1: Team review and progress meetings

    80% Completed.

    Milestone: Agreement on eligibility criteria, screening protocol and procedure – Completed.

    (Note: Progress reviews and medical reviews will continue as the protocol is ongoing. All other subtasks in the SOW have been completed for task 1.)

  - Task 2: Submission of Documents for Regulatory Approvals

    100% Completed.

  - Task 3: Start up

    100% Completed.

    Milestone: Protocol ready to begin-Completed.

- Task 4: Advertisement

  60% Completed. New recruitment tools have been launched and are actively ongoing. A recruiting event was held in March 2016 at the Birmingham Jefferson Civic Center (BJCC) in Birmingham, Alabama. Radio advertisements (subtask 1) were aired May 2, 2016-May 27, 2016 and August 8, 2016-September 8, 2016, and a third round of advertising was completed May 22, 2017-June 29th 2017 The recruitment webpage (subtask 2) has been published, and 222 individuals have filled out the online screening questionnaire linked from the webpage.

  Milestone: 120 potential participants screened by telephone—100% Completed. As of 10/6/2017, one-hundred and twenty-nine potential participants have been screened by telephone.

  (Note: Telephone pre-screenings will continue until the desired number of participants have enrolled into the study.)

  (Note: Birmingham VA recruitment (subtasks 3, 4, & 5) will be initiated in 2017 or as needed.)

- Task 5: Screen GWI participants for study

  82.5% Completed. Thirty-three individuals have signed consent and enrolled into the study. Twenty-three participants have been randomized; five have been excluded based on screening lab tests; two have been excluded for major PTSD symptoms; four have withdrawn from the protocol (two before randomization and two after); one participant was investigator-withdrawn mid-way through the protocol due to non-compliance, and one is pending re-screening. Five more potential participants have been determined to meet initial eligibility requirements and are pending in-person screening visits and enrollment.

  Milestone: First participant enrolled—Completed.

  Milestone: 40 GWI participants enrolled- 82.5% Completed

- Task 6: Run protocol

  10% Completed.

  Milestone: *First four participants successfully completed the protocol*-Completed.

  (Note: Task progress is ongoing and is dependent on the completion of Task 5.)

- Task 7: Assays

  0% Completed.

  (Note: Task progress is dependent on the completion of Tasks 5 & 6.)

- Task 8: Analysis

  0% Completed.

  (Note: Task progress is dependent on the completion of Tasks 6 &7.)

- Task 9: Preparation of Final report and Publications

  0% Completed.

  (Note: Task progress is dependent on the completion of Tasks 6, 7, & 8.)

- **What opportunities for training and professional development has the project provided?**

  Nothing to report.

- **How were the results disseminated to communities of interest?**

  Nothing to report.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  The focus during the next reporting period will be on **Task 4: Advertisement** and **Task 5: Screen GWI participants for study.** As noted above, advertisement is ongoing, and an additional round of radio advertisements will be scheduled in the upcoming months. Screening and enrollment are ongoing as well. Recently, the study coordinators have spoken at several local Disabled American Veterans chapters to let local veterans know about the opportunity to participate. Every effort is being made to enroll the potential participants identified as meeting initial eligibility requirements as a result of our prescreening process and to work toward protocol completion.

4. **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

  Nothing to report.

- **What was the impact on other disciplines?**

  Nothing to report.

- **What was the impact on technology transfer?**

  Nothing to report.

- **What was the impact on society beyond science and technology?**

  Nothing to report.

5. **CHANGES OR PROBLEMS:**

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  During the last reporting period, we have had several individuals withdraw from the study protocol. In most of these cases, participants have cited hectic work schedules and an inability to take off work as the cause for their withdrawal. Changes in work schedules is a problem we are not able to anticipate, but every effort is being made to ensure participants are made aware of their expected commitment at the beginning of the study. Due to these withdrawals, we will need to recruit additional individuals to reach our target number of participants taking each botanical.

  In addition to participant withdrawals, we have had a 1:4 Screen Failure ratio. Meaning, for every four people we bring in for an in-person screening visit, one still does not meet criteria for the study. This is a problem we anticipated and budgeted for, but identifying additional participants takes time.

6. **PRODUCTS:**

- **Publications, conference papers, and presentations**

  - **Journal publications.**

    Nothing to report.

  - **Books or other non-periodical, one-time publications.**

    Nothing to report.

  - **Other publications, conference papers, and presentations.**

    Cobb, J.D., Donovan, E.K., & Younger, J.W. (2017, April). *Deployment duration does not predict symptom severity in men with Gulf War Illness.* Poster Presented at the 2017 UAB Ost Research Competition, University of Alabama at Birmingham, Birmingham, AL, USA.

    Donovan, E.K., Massey, R.L., & Younger, J.W. (2016, October*) Diagnostic overlap of Gulf War Illness, Myalgic Encephalomyelitis/ Chronic Fatigue syndrome, and Fibromyalgia in Gulf War Veterans.* Poster presented at the University of Alabama at Birmingham (UAB) Pain Symposium 2016, Birmingham, AL, USA.

    Massey, R.L., Donovan, E.K., & Younger, J.W. (2016, July) *Effects of Botanical Microglia Modulators in Gulf War Illness: A Novel Screening Approach.* Poster presented at the University of Alabama at Birmingham (UAB) Summer Expo 2016, Birmingham, AL, USA.

- **Website(s) or other Internet site(s)**

  Nothing to report.

- **Technologies or techniques**

  Nothing to report.

- **Inventions, patent applications and/or licenses**

  Nothing to report.

- **Other Products**

  Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

Name	Jarred Younger
Project Role	PI
Research Identifier	
Nearest person month worked	2.5 CM
Contribution to Project	Dr. Younger continues to review telephone screens and consult with Emily on potential participant eligibility and inclusion criteria as well as other project questions during a weekly meeting. Dr. Younger has also advised on additional recruitment and advertising methods. He continues to conduct informative broadcast sessions in an effort to increase community awareness and participant recruitment.

Name	Tammie Quinn
Project Role	Lab manager
Research Identifier	
Nearest person month worked	2 CM
Contribution to Project	Tammie has assisted with recruitment and pre-screening efforts by maintaining the UAB LISTSERV to send out newsletters and updated study recruitment materials to interested individuals and support groups. Also, she prepared and submitted UAB IRB annual review and HRPO/ORP continuing review documents.

Name	Emily Donovan
Project Role	Coordinator
Research Identifier	
Nearest person month worked	12 CM
Contribution to Project	Emily has maintained recruitment efforts by communicating with VA support group and community leaders for recruiting purposes. She has reviewed 222 prescreening questionnaires and has conducted 129 telephone prescreening to identify the 33 potentially eligible participants she has conducted in-person screenings for.

8. **SPECIAL REPORTING REQUIREMENTS:**

None.

9. **APPENDICES:**

None.